Deciphering the response and resistance to immunecheckpoint inhibitors in lung cancer with artificial intelligence-based analysis: the pioneer and quantic joint-projects

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DECIPHERING THE RESPONSE AND RESISTANCE TO IMMUNECHECKPOINT INHIBITORS IN LUNG CANCER WITH ARTIFICIAL INTELLIGENCE-BASED ANALYSIS: THE PIONEER AND QUANTIC JOINT-PROJECTS.

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Running Title: The PIONeeR and QUANTIC joint-project.

Abstract

Despite striking results, clinical outcome with immune checkpoint inhibitors remains too often uncertain. This joint-project aims at generating dense longitudinal data in lung cancer patients undergoing anti-PD1 or anti-PDL1 therapy, alone or in combination with other anticancer agents. Mathematical modelling with mechanistic learning algorithms will be used next to decipher the mechanisms underlying response or resistance to immunotherapy. Ultimately, this project should help to better understand the mechanisms underlying resistance to immune checkpoint inhibitors and identify a serial of actionable items to increase the efficacy of immunotherapy.

The era of precision medicine mostly relies on identifying biomarkers likely to help oncologists forecasting clinical outcome. Immune checkpoint inhibitors are game-changing drugs in oncology, as some cancers with once dismal prognosis show now survival rates that count in years. Non-small cell lung cancer is typically a disease which clinical outcome has been dramatically improved over a short period of time with first targeted therapies and then the successive approvals of anti-PD1 and anti-PDL1 biologics (1). However, after the initial frenzy ignited by promising phase-3 trials with nivolumab, pembrolizumab or more recently atezolizumab, alone or in combination with standard chemotherapy, many questions remain unsolved. In particular, the lack of robust and fully validated biomarkers for predicting response to immune checkpoint inhibitors (ICIs) remains a major issue. PDL1 expression, tumor mutational burden, initial tumor size, history of steroids or antibiotics use, MSI status, gut microbiota characteristics have all been pointed independently as possible factors impacting on response or survival in patients treated next with ICIs (2-4). However, many uncertainties remain, essentially because of possible confounding factors, and the lack of global understanding of the utterly complex interplay between drugs, immune system, tumor cells, tumor micro-environment, plus all physio-pathological parameters and patients characteristics likely to interfere with harnessing tumor immunity (5). Consequently, in many respect treating patients with immunotherapy looks like a big lottery - the winning tickets (i.e., response or remission with no or little immune-related toxicities) being apparently distributed randomly among patients (6). In this context, association between clinical investigators, biologists, mathematicians and industrials is crucial to accurately exploit big clinical and biomarkers data and stratify patients prior to therapeutic decision. The PIONeeR project is built upon a large biomarkers program and a randomized, umbrella clinical trial aiming at understanding, predicting and overcoming resistance to PD1 and PDL1 immune checkpoint

inhibitors. The study (NCT03493581) first investigates a wide panel of putative tissue and liquid biomarkers aiming at deciphering the immune contexture in 450 advanced lung cancer patients treated with either nivolumab, pembrolizumab or atezolizumab alone or in combination with chemotherapy. Tested biomarkers include advanced immunohistochemistry coupled to digital pathology analyses such as CD8+/PDL1+ co-localization (Immunoscore®) or complex immune cell populations localization and quantification including Myeloid Derived Suppressor Cells, blood immune-monitoring including rare cell subsets, genomics and transcriptomics, gut microbiota exploration, , study of vascular factors, pharmacokinetics and PK/PD modelling. Both progressors and responding patients are closely monitored so as to better uncover unbiased predictive biomarkers. Patients with progressive disease before 24 weeks of treatment will be next further randomized in a second clinical step testing at least 3 combinatorial regimens of targeted therapies with anti-PDL1 durvalumab with full longitudinal monitoring as well. The primary objective is to highlight immune algorithms predicting anti-PD1/L1 primary and adaptive resistance to stratify patients prior to ICI treatment. Importantly, all the collected data will be used next as part of the QUANTIC add-on project, which is an original collaboration between French National Institute for Research on Computer Science and Applied Mathematics (best known as INRIA) and the PIONeeR consortium. The primary objective of QUANTIC is to develop and validate a mechanistic, dynamic model of response and resistance to immune-checkpoint inhibition leveraging the unique, large scale, multi-modal and longitudinal data collected during the PIONeeR clinical study. Indeed, artificial intelligence techniques are required to analyze the ”big data” generated by PIONeeR (e.g., immunomonitoring alone will result in hundreds of quantitative variables per time point, per patient) plus additional APHM routine patients (i.e., 521 NSCLC patients that have received anti-PD1/PDL1 treatment over

the last 5 years). On the other hand, mechanistic modelling consists in designing physiologically-based mathematical constructs for the systemic kinetics of the disease and its response to ICIs. Such models have superior value to artificial intelligence algorithms because they are interpretable. This allows them to account for the biological meaning of part of the data (e.g. quantification of immune players) and to test biological hypotheses, which improves our mechanistic understanding of the processes at play. However, the fact that not all the data have a biological meaning, combined to the large number of variables in some data modalities (e.g., genomics or immune-monitoring), as well as the requirement for nonlinear covariate models are all rationales to keep parts of the modelling biologically agnostic, i.e. relying on machine learning alone. As stated above, the major clinical challenge with immunotherapy today is the wide inter-individual heterogeneity in response to ICIs. To address this issue and quantify this variability, mixed-effects statistical learning will be used for the first time. All patients' data will be pooled together for the learning process, which strengthens estimation of the mechanistic parameters. Machine learning for inclusion of baseline covariates will further yield new algorithms able to predict the response/relapse patterns, including possible pseudo- or hyper- progression. Finally, model parameters and longitudinal analysis will be used to predict overall survival. This unique and entire multi-modal framework for mechanistic description and prediction of longitudinal kinetics of hundreds of coupled biomarkers will go much beyond the current state-of-the art in clinical quantitative modeling since most of the current studies model only the sum of longest diameters from RECIST target lesions as readouts.

Overall, the PIONeeR and QUANTIC projects highlight how state-of-the art computational oncology, biomarker-based investigations and clinical trials should join their forces for deciphering the complex mechanisms explaining the variability in clinical outcomes with

immunotherapy (7). As such, it should bring substantial progress for in depth understanding of resistance to ICIs in advanced lung cancer patients. The final mathematical models will be used in the future as a new powerful tool for decision-making, i.e. by clustering patients prior to start the immunotherapy through a unique combination of somatic and germinal traits. In addition, depending on the actionable items that will have emerged from the project (e.g., drug exposure parameters calling for adaptive dosing strategies), patients once doomed to progress upon immunotherapy will benefit from customized treatment so as to increase their odds of success.

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